METHOD OF PRODUCING A MULTICOMPONENT LYOPHILIZED PRODUCT

Filed Oct. 31, 1969

FIG. 1

FIG. 2

FIG. 3

FIG. 4
METHOD OF PRODUCING A MULTICOMPONENT LYOPHILIZED PRODUCT

Eugene S. Barclay, West Chester, Pa., assignor to Merck & Co., Inc., Rahway, N.J.
Filed Oct. 31, 1969, Ser. No. 873,111

Int. Cl. F26b 5/06
U.S. Cl. 34—5

ABSTRACT OF THE DISCLOSURE

A solution is charged to a container, the solution is frozen, the container is rotated about an axis in such a manner that a second solution introduced to the container does not come in contact with the frozen first solution and then it is frozen. This process is repeated as often as desired or as often as the relative sizes of the container and solution volumes will permit. The frozen masses are then simultaneously lyophilized.

This invention relates to a method of packaging a plurality of lyophilized components in a single container in which no component is in contact with another component. The method finds its principle utility wherein incompatibility exists between any of the components in the presence of moisture. The invention also relates to the package produced by the novel process of this invention.

An object of this invention is the provision of a dry product including two or more components each adjacent another arrayed about and adhered to the wall of a single container. Another object is the provision of a package consisting of a container having received therein at least two adjacent masses of lyophilized materials in which at least one of such masses includes a substance different from that contained in another of such masses. A special object is to provide a pharmaceutical package as described in which each of such masses includes a biological or physiological factor.

In industry in general, and particularly the chemical and pharmaceutical industries it is often desirable to supply products consisting of more than one component. Occasionally it is found that the components making up a given product are incompatible with each other to some extent either prohibiting their preparation as a single multicomponent system or at least shortening the storage life of the multicomponent product. In such cases it is necessary that the components be sold in separate containers and used individually or mixed immediately before use by the consumer. This is especially true in the pharmaceutical industry where the multicomponent products contain physiological or biological materials which are incompatible one with another, particularly when the products are to be given by injection.

Examples of multicomponent products useable in the novel procedure of this invention are those containing vitamin B12, an anti-anemia liver concentrate, and folie acid. Another system is adenocorticotropic substances and vitamin B12. Additional examples are multivalent vaccines such as one containing measles, mumps and rubella antigens.

The prior art, U.S. Pat. 3,269,905, has attempted to solve this problem by admitting to a container a first component, freezing, admitting a second component on top of the first, freezing, admitting a third component on top of the second and freezing and then lyophilizing the entire mass to produce a stratified lyophilized product, each stratum being of a single component. This procedure has a shortcoming in that for a time during the process there is the possibility of interaction between two components at the interface between one frozen component and a newly added liquid component.

The present invention obviates this shortcoming by providing that the various components are never in contact with one another either in the frozen, liquid or lyophilized states. The process of the present invention contemplates adding a solution of a first component to a container and freezing the solution on the wall of the container. The position of the container is then changed so that when a solution of a second component is added thereto it is adjacent but not touching the first frozen component. This second solution is then frozen in its position. This process is repeated for as many different components as required by the particular product.

For a more detailed explanation of the invention reference is made to FIGS. 1 to 4. FIGS. 1 and 2 represent the process in two views. The container 1 with a means 2 for introducing a liquid composition is immersed in a freezing bath 3. After the first liquid composition 4 has been introduced and frozen, the container 1 is rotated, and a second liquid composition 5 is introduced slowly. FIG. 3 represents the container 1 with two frozen compositions 4 and 5 connected to a means 7 for applying a high vacuum for the lyophilization step. FIG. 4 is a cross-sectional view of the container 1 with three frozen or lyophilized compositions 4, 5 and 8.

An example of this method for preparing a multivalent vaccine involves adding to a sterilized 10 cc. pharmaceutical vial 1.5 ml of sterile measles vaccine. The vial is then laid on its side in a freezer chest at a temperature of about 60° C. until the liquid is frozen. The vial is rotated through 120° and 1.5—2.0 ml of sterile mumps vaccine is added and it is frozen as described above. The vial is rotated through another 120° and a third solution consisting of 1.5—2.0 ml of rubella vaccine is added and then frozen. The contents of the vial is then lyophilized in the usual manner to provide a sterile, dry multivalent vaccine. The lyophilized product obtained in this process can be reconstituted with a liquid vehicle to produce a multivalent vaccine suitable for parenteral injection.

What is claimed is:

1. A process for obtaining a package containing at least two masses of dry matter which comprises the steps of charging a first liquid composition into a container, freezing said composition, rotating said container about an axis, charging to said container a second liquid composition adjacent but not touching the frozen first composition, freezing said second liquid composition, and simultaneously lyophilizing the frozen masses.

2. The process of claim 1, wherein each of the materials charged into the container is a liquid composition of a pharmaceutical agent.

3. The process of claim 1, wherein each of the materials charged into the container is a liquid composition of an antigen suitable for use in a multivalent vaccine.
4. The process of claim 1 wherein one of the materials charged into the container is a liquid composition of vitamin B₁₂, wherein another of the materials is a solution or suspension of folic acid, and another of the materials is a solution or suspension of anti-anemia liver concentrate.

5. The process of claim 1, wherein one of the materials charged into the container is a liquid composition of adrenocorticotrophin and another of the materials charged is a solution or suspension of vitamin B₁₂.

6. The process of claim 1 wherein the container is a glass pharmaceutical vial.